

HEAD AND NECK

CHAPTER 21

The Pupils

KEY TEACHING POINTS

- Problems in the *afferent* half of the pupillary light reflex (e.g., optic neuropathy) produce *symmetric* pupils. Only the swinging flashlight test uncovers the afferent abnormality in these patients (i.e., the Marcus Gunn pupil or relative afferent pupillary defect).
- Problems in the *efferent* half of the pupillary light reflex produce *unequal* pupils (anisocoria). Possible causes include parasympathetic or sympathetic denervation, pharmacologic mydriasis, or disorders of the iris.
- In patients with anisocoria (efferent disease), the *pupillary constrictor* of the *larger* pupil is abnormal if the anisocoria is more pronounced in a brightly lit room (compared with a darkened room) or if the larger pupil reacts poorly to light. Possible diagnoses are third nerve palsy, tonic pupil, pharmacologic mydriasis, or abnormal iris.
- In patients with anisocoria, the *pupillary dilator* of the *smaller* pupil is abnormal if the anisocoria is worse in a darkened room (compared with a brightly lit room) or if both pupils react well to light. Possible diagnoses are Horner syndrome or simple anisocoria.
- Examination of pupils is fundamental in the evaluation of patients with visual blurring, visual field defects, coma, stroke, third cranial nerve palsy, red eye, supraclavicular or lung masses, or neck pain.

NORMAL PUPIL

I. INTRODUCTION

The integrity of the pupil depends on the iris, cranial nerves II and III, and the sympathetic nerves innervating the eye.

II. SIZE

The size of the normal pupil decreases as persons grow older ($r = -0.75$, $p < 0.001$): at 10 years of age the mean diameter is 7 mm, at 30 years it is 6 mm, and at 80 years

it is 4 mm.^{1,2} Throughout human history, large pupils have been associated with youth, beauty, and vigor, explaining why the plant yielding the pupillary dilator atropine was named *belladonna*, which literally means “beautiful lady.”

III. HIPPIUS

Under steady illumination the normal pupil is in continual motion, repeatedly dilating and contracting small amounts. This restless undulation, called **hippus** or **pupillary unrest**, is more prominent in younger patients and during exposure to bright light. Clinicians of the 19th century associated hippus with diverse disorders, ranging from myasthenia gravis to brain tumors, but hippus is now known to be a normal phenomenon.³ The oscillations of the right and left pupil are synchronous, which suggests hippus is under central control.

IV. SIMPLE ANISOCORIA

Simple anisocoria, a normal finding, is defined as a difference in pupil diameter of 0.4 mm or more that cannot be attributed to any of the pathologic pupils discussed later, intraocular drugs, ocular injury, or ocular inflammation.² Simple anisocoria affects up to 38% of healthy persons (only half of whom have anisocoria at any given moment) and is a constant finding in 3% of persons. As simple anisocoria waxes and wanes over time, it is the usually same eye that displays the larger pupil.²

The difference in pupil size in simple anisocoria rarely exceeds 1 mm.² Other features distinguishing it from pathologic anisocoria are described later, under the section on Abnormal Pupils.

V. NORMAL LIGHT REFLEX

A. ANATOMY

Fig. 21.1 illustrates the nerves responsible for the normal light reflex. Because both pupillary constrictor muscles normally receive identical signals from the midbrain, they constrict the same amount, which may be small or large depending on the *summation* of light intensity coming into *both* eyes. For example, both pupils dilate the same amount in darkness, constrict an identical small amount when a dim light is held in front of one eye, and constrict an identical larger amount when a bright light is held in front of one eye.

With a light held in front of one eye, ipsilateral pupillary constriction is called **direct reaction** to light and contralateral constriction is called **consensual reaction**.

B. CLINICAL SIGNIFICANCE

The anatomy of the normal light reflex has two important clinical implications:

1. **Anisocoria Is Absent in Disorders of the Optic Nerve or Retina (i.e., Afferent Connections).** Because the signal in both outgoing third nerves is identical in these disorders, representing the summation of light intensity from both eyes, the pupils are the same size. Unilateral afferent disease is similar to the experiment of holding a bright light in front of one eye (i.e., the opposite eye thus mimicking one with an afferent defect): despite the asymmetry of light signals in the two optic nerves, both pupils have identical diameter.
2. **Anisocoria Indicates Asymmetric Disease of the Iris, Cranial Nerve III, or Sympathetic Nerves (Efferent Connections and Iris).** Asymmetric disease of the efferent connections guarantees that the signals arriving at the pupil are different and therefore that the pupil size will be different.

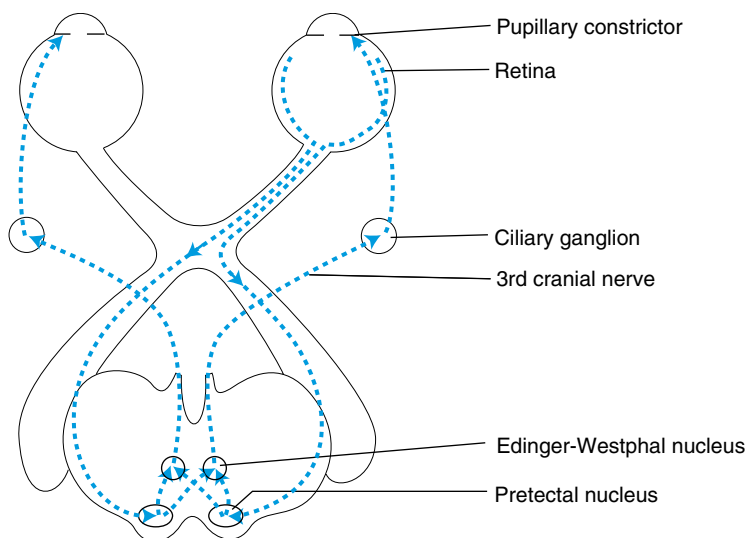


FIG. 21.1 ANATOMY OF THE PUPILLARY LIGHT REFLEX. The *dotted lines* show how nerve impulses from the retina and optic nerve on one side (right eye in this example) contribute to the nerve impulses of both third nerves, via the crossing of the nerve impulses from the nasal retina in the optic chiasm and the abundant interconnections between both pretectal nuclei and both Edinger-Westphal nuclei. Unless there is asymmetric disease of the efferent pathway (i.e., third nerve, ciliary ganglion and postganglionic fibers, iris), the pupils are thus symmetric.

VI. NEAR SYNKINESIS REACTION

The near synkinesis reaction occurs when a person focuses on a near object. The reaction has three parts: (1) constriction of the pupils (pupilloconstrictor muscle), (2) convergence of eyes (medial rectus muscles), and (3) accommodation of the lenses (ciliary body).

ABNORMAL PUPILS

I. RELATIVE AFFERENT PUPILLARY DEFECT (MARCUS GUNN PUPIL)

A. INTRODUCTION

The relative afferent pupillary defect is the most common abnormal pupillary finding, more common than all other pupillary defects combined.⁴

Although the relative afferent pupillary defect was described by R. Marcus Gunn in 1904, it is clear from his report that the sign was generally known to clinicians of his time. Kestenbaum named the finding in 1946 after Marcus Gunn,⁴ and in 1959 Levatin introduced the swinging flashlight test, which is how most clinicians now elicit the finding.⁵

B. THE FINDING

Because the pupils are equal in patients with disorders of the retina and optic nerves (see the section on Normal Pupils, earlier, and Fig. 21.1), the **swinging flashlight test** is necessary to uncover disorders of the afferent half of the light reflex. This test compares the amount of pupilloconstriction produced by illuminating one eye with that produced by illuminating the other.

To perform the test, the clinician swings the flashlight back and forth from eye to eye, holding it over each pupil 1 to 3 seconds before immediately shifting it to the other (Fig. 21.2). Both pupils constrict strongly when the light is shining into the normal eye, but, as the light swings over to illuminate the abnormal eye, both pupils dilate (dilation occurs because the pupils respond as if the light were much dimmer, producing less bilateral constriction—or net dilation—compared with when the light is shining in the normal eye).^{4,6} As long as the clinician swings the light back and forth, the reaction persists—pupils constrict when illuminating the normal eye and dilate when illuminating the abnormal eye. Because clinicians usually focus on the illuminated pupil, the one that dilates is labeled as having a **relative afferent pupillary defect**, or the **Marcus Gunn pupil**.

There has been some debate whether eyes with afferent defects also display abnormal **pupillary release** (i.e., the small amount of pupillary dilatation immediately following initial constriction during steady illumination).⁷ Nonetheless, two studies demonstrated that only the swinging flashlight test reliably uncovers the afferent defect.^{8,9}

Light reflecting off the cornea may sometimes obscure the movements of the pupils. To overcome this, the clinician should angle the light by holding the light source slightly below the horizontal axis.

Interpreting the swinging flashlight test has three caveats⁶:

1. **Correct interpretation of the test ignores hippus**, which otherwise can make interpretation difficult.
2. **The clinician should avoid the tendency to linger with the flashlight on the eye suspected to have disease.** Uneven swinging of the light may temporarily bleach the retina being illuminated more, thus eventually producing a relative pupillary defect and erroneously confirming the initial suspicion. To avoid this and ensure equal illumination of both retinas, the clinician should silently count: “one, two, switch, one two, switch,” and so on.
3. **Only one working iris is required to interpret this pupillary sign.** If the patient has only one pupil that reacts to light (see the section on Anisocoria), the test is performed the same way, although the clinician focuses only on the normal iris to interpret the results.

C. CLINICAL SIGNIFICANCE

A relative afferent defect implies ipsilateral optic nerve disease or severe retinal disease.

I. OPTIC NERVE DISEASE

Patients with optic nerve disease (e.g., optic neuritis, ischemic optic neuropathy, glaucomatous optic nerve damage) have the most prominent relative afferent pupillary defects. If the disease is asymmetric, the sensitivity of the finding is 92% to 98%, much higher than that for other tests of afferent function, including visual acuity, pupil cycle times, appearance of optic disc during funduscopy, and visual evoked potentials.^{10,11} Even compared with optical coherence tomography, the Marcus Gunn pupil is accurate, detecting the asymmetric thickness of the retinal nerve fiber layer in patients with glaucoma (sensitivity = 92%, specificity = 78%, positive likelihood ratio [LR] = 4.2, negative LR = 0.1)¹² and multiple sclerosis (sensitivity = 50%, specificity = 86%, positive LR = 3.6).¹³

Even so, the Marcus Gunn pupil depends on *asymmetric* optic nerve function (hence the word *relative* in its label); consequently, if patients with suspected

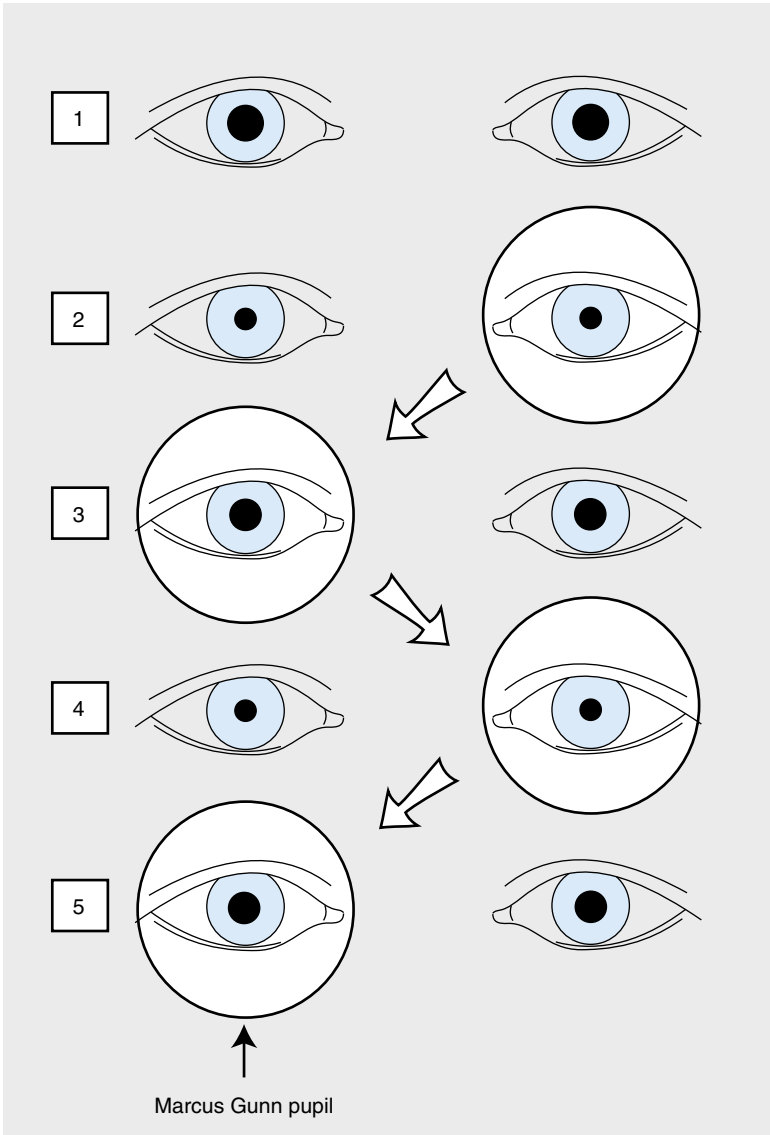


FIG. 21.2 THE RELATIVE AFFERENT PUPILLARY DEFECT (MARCUS GUNN PUPIL). The figure depicts a patient with an abnormal *right* optic nerve. Under normal room light illumination (row 1), the pupils are symmetric. During the swinging flashlight test, the pupils constrict when the normal eye is illuminated (rows 2 and 4) but dilate when the abnormal eye is illuminated (rows 3 and 5). Although both pupils constrict or dilate simultaneously, the clinician is usually focused on just the illuminated pupil. The pupil that dilates during the swinging flashlight test has the relative afferent pupillary defect and is labeled the Marcus Gunn pupil. See the text.

unilateral disease lack the afferent pupillary finding, bilateral optic nerve disease is eventually found in 65%.¹¹

2. RETINAL DISEASE

Severe retinal disease may cause a relative afferent pupillary defect, although the retinal disease must be markedly asymmetric to produce the finding and, once the finding appears, it is subtle compared with that seen in optic nerve disease.¹⁴

3. CATARACTS DO NOT CAUSE THE RELATIVE AFFERENT PUPILLARY DEFECT¹⁵

Although this seems surprising, it is because the retina, if healthy, compensates over minutes for any diminished brightness, just as it does after a person walks into a dark movie theater. In fact, during the time of Galen, the classical Roman physician, clinicians tested the pupillary light reaction of patients with cataracts to determine whether vision could be restored after couching (couching was an ancient treatment for cataracts that used a needle to displace the cataract posteriorly; a preserved light reaction indicated that the retina and optic nerve behind the cataract were intact).¹⁶

II. ARGYLL ROBERTSON PUPILS

A. THE FINDING^{17,18}

Argyll Robertson pupils have four characteristic findings: (1) bilateral involvement, (2) small pupils that fail to dilate fully in dim light, (3) no light reaction, and (4) brisk constriction to near vision and brisk redilation to far vision.

Originally described by Douglas Moray Cooper Lamb Argyll Robertson in 1868, this finding had great significance a century ago because it settled a long-standing debate whether general paresis and tabes dorsalis were the same disease. The pupillary abnormality was found in a high proportion of patients with both diseases and was limited to these diseases, arguing for a common syphilitic origin of both. The introduction of the Wasserman serologic test for syphilis in 1906 confirmed that the two diseases had the same cause.

B. CLINICAL SIGNIFICANCE

1. ASSOCIATED DISORDERS

In addition to neurosyphilis, there are rare, scattered reports of Argyll Robertson pupils in patients with various other disorders, including diabetes mellitus, neuro-sarcoidosis, and Lyme disease (see the section on Diabetic Pupil).¹⁷ The responsible lesion is probably located in the dorsal midbrain, where damage would interrupt the light reflex fibers but spare the more ventrally located fibers innervating the Edinger-Westphal nuclei that control the near reaction.^{19,20}

2. DIFFERENTIAL DIAGNOSIS OF LIGHT-NEAR DISSOCIATION

Argyll Robertson pupils display light-near dissociation (i.e., they fail to react to light but constrict during near vision). Other causes of light-near dissociation include the following:

1. Adie Tonic Pupil (see later).
2. Optic Nerve or Severe Retinal Disease. Either of these disorders may eliminate the light reaction when light is directed into the abnormal eye, although the pupils still constrict with the near synkinesis. However, in contrast to other causes of light-near dissociation, optic nerve and retinal disease severely impair vision.

3. Dorsal Midbrain Syndrome (Parinaud syndrome, Sylvian Aqueduct Syndrome, Pretectal Syndrome).²¹ Characteristic findings of the dorsal midbrain syndrome are light-near dissociation, vertical gaze palsy, lid retraction, and convergence-retraction nystagmus (a rhythmic inward movement of both eyes from cocontraction of the extraocular muscles, usually elicited during convergence on upward gaze; many neuro-ophthalmologists use a optokinetic drum rotating downward to elicit the finding). Common causes of the dorsal midbrain syndrome are pinealoma in younger patients and multiple sclerosis and basilar artery strokes in older patients.
4. Aberrant Regeneration of the Third Nerve. After damage to the third nerve (from trauma, aneurysms, or tumors, but *not* ischemia), regenerating fibers originally destined for the medial rectus muscle may instead reinnervate the pupillary constrictor, thus causing pupillary constriction during convergence but the absence of reaction to light. However, unlike Argyll Robertson pupils, this finding is unilateral, and most patients also have anisocoria, ptosis, and diplopia.²²

3. NEAR-LIGHT DISSOCIATION

The phenomenon opposite to light-near dissociation, **near-light dissociation**, describes pupils that react to light but not during near synkinesis. Near-light dissociation was historically associated with von Economo encephalitis lethargica, although experts now believe it indicates that the patient is not trying hard enough to focus on the near object.¹⁷ For this reason, many neuro-ophthalmologists save time during their examination and skip testing the near response unless the patient demonstrates no pupillary light reaction.

III. OVAL PUPIL

There are three causes of the oval pupil.

A. EVOLVING THIRD NERVE PALSY FROM BRAIN HERNIATION

These patients are invariably comatose from cerebral catastrophes causing elevated intracranial pressure.^{23,24} As the pupil enlarges, it may appear oval for a short time before it becomes fully round, dilated, and fixed.

B. ADIE TONIC PUPIL (SEE LATER)

The Adie tonic pupil may sometimes appear oval from segmental iris palsy.²⁵ These patients are alert and, if complaining of anything, describe blurring of vision in the involved eye (from paralysis of accommodation).

C. PREVIOUS SURGERY OR TRAUMA TO THE IRIS

IV. ANISOCORIA

A. DEFINITION

Anisocoria is defined as a difference of 0.4 mm or more in the diameter of the pupils. It represents either a problem with the pupillary constrictor muscle (parasympathetic denervation, iris disorder, pharmacologic pupil) or the pupillary dilator muscle (sympathetic denervation, simple anisocoria).

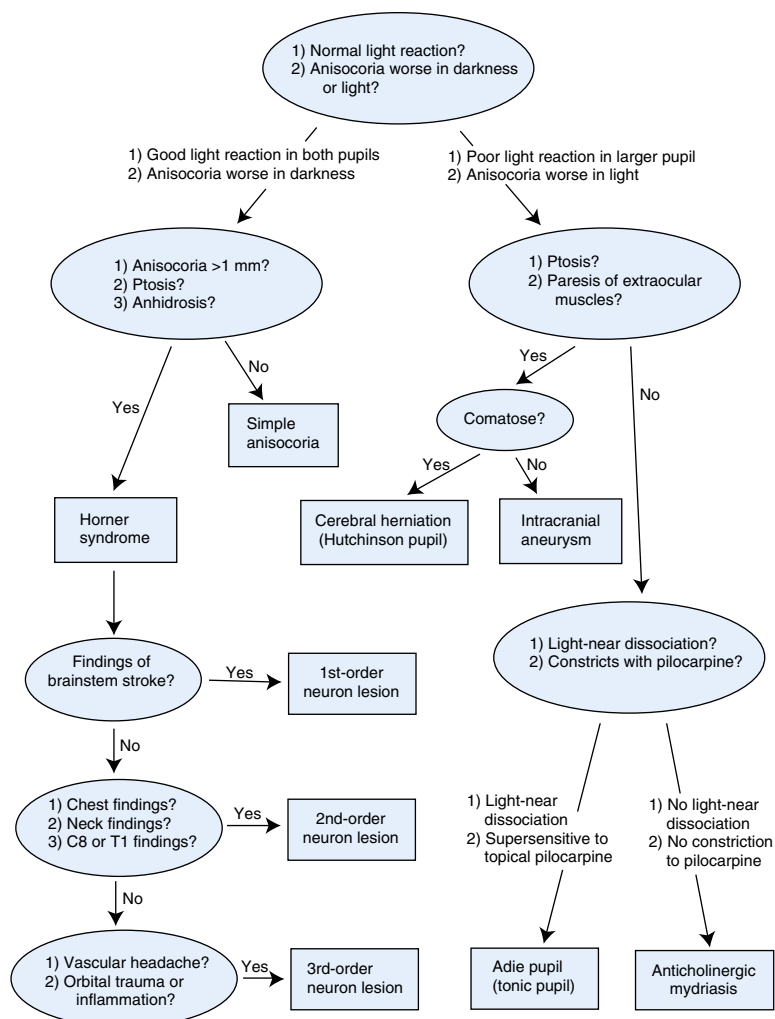
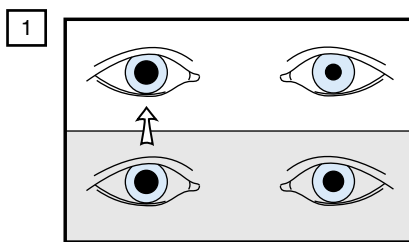


FIG. 21.3 SUMMARY OF APPROACH TO ANISOCORIA. The first two questions (Is there a normal light reaction? and Is anisocoria worse in darkness or light?) (see also Fig. 21.4) distinguish problems with the pupillary dilator muscle (i.e., Horner syndrome, simple anisocoria; *left side* of the figure) from problems with the pupillary constrictor muscle (i.e., third cranial nerve, iris; *right side* of the figure). Two other tests distinguish Horner syndrome from simple anisocoria: the cocaine or apraclonidine eyedrop tests (see the text) and pupillary dilator lag (i.e., the pupil dilates slowly in darkness, as documented by photographs; see the text). (Based upon references 26 and 27.)

Anisocoria worse in *light*;
pupillary constrictor abnormal



Anisocoria worse in *darkness*;
pupillary dilator abnormal

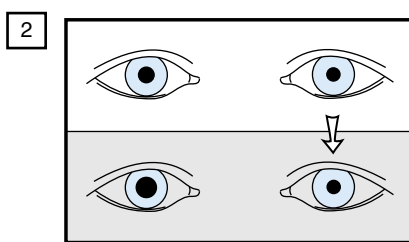


FIG. 21.4 COMPARING ANISOCORIA IN LIGHT AND DARKNESS. Patient 1 (*top*) has more prominent anisocoria in light than darkness, indicating that the pupillary constrictor of the *larger* pupil is abnormal (i.e., it fails to constrict in light, *arrow*). Patient 2 has more prominent anisocoria in darkness than light, indicating that the pupillary dilator of the *smaller* pupil is abnormal (i.e., it fails to dilate in darkness, *arrow*). The diagnosis in patient 1 (abnormal pupillary constrictor) could be a third nerve palsy, tonic pupil, pharmacologic mydriasis, or a disorder of the iris (*right side of Fig. 21.3*). The diagnosis in patient 2 (abnormal pupillary dilator, *left side of Fig. 21.3*) could be Horner syndrome or simple anisocoria. In patient 2, both pupils will react to light, whereas the larger pupil of patient 1 does not react well to light.

B. TECHNIQUE

Figs. 21.3 and 21.4 summarize the initial approach to anisocoria.^{26,27} The most important initial questions follow:

1. **Is Anisocoria Old or New?** Examination of a driver's license photograph or other facial photograph, magnified with the direct ophthalmoscope (using the +10 lens), may reveal a preexisting pupillary inequality.²⁸
2. **Do Both Pupils Constrict Normally During the Light Reflex?** If there is a poor light reaction in the eye with the larger pupil, the pupillary constrictor of that eye is abnormal. If there is a good light reaction in both eyes, the pupillary dilator of the eye with the smaller pupil is abnormal.
3. **Is Anisocoria Worse in Bright Light or Dim Light/Darkness?** If anisocoria is worse in light than darkness, the pupillary constrictor of the eye with the larger pupil is abnormal. If anisocoria is worse in darkness than light, the pupillary dilator of the eye with the smaller pupil is abnormal (see Fig. 21.4).^{29 *}

*To determine the amount of anisocoria in darkness, neuro-ophthalmologists often take flash photographs of patients in darkness. Because there is a delay of approximately 1.5 seconds between the flash of light and subsequent pupillary constriction, a photograph that is synchronous with the initial flash will actually reflect pupil size in darkness (this delay explains why modern cameras reduce “red eye” by flashing repeatedly before the photograph is taken).⁴

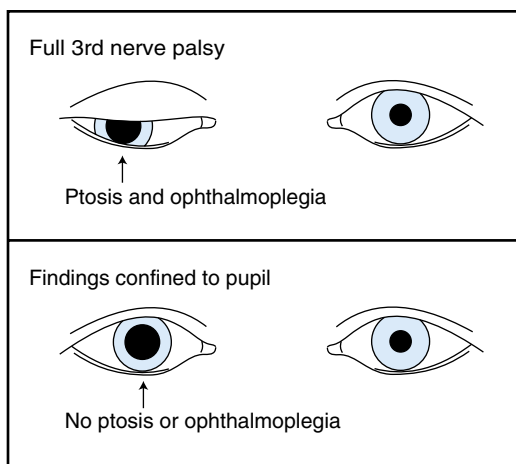


FIG. 21.5 TYPES OF ABNORMAL PUPILLARY CONSTRICTOR. Both patients in this figure have a paralyzed right pupillary constrictor (i.e., a dilated pupil that fails to react well to light; see Fig. 21.4). The patient in the top row also has ptosis and ophthalmoplegia (i.e., eyes not aligned), indicating a full third nerve palsy; possible diagnoses are transtentorial herniation (if comatose) or intracranial aneurysm (if mentally alert). The patient in the bottom row lacks ptosis and ophthalmoplegia, indicating the findings are confined to the pupil itself: possible diagnoses are the tonic pupil, pharmacologic mydriasis, or a disorder of the iris. See the text.

C. ABNORMAL PUPILLARY CONSTRICTOR MUSCLE

If an abnormal pupillary constrictor muscle is present, the *fixed, dilated pupil* is due to parasympathetic defect, iris disorder, or pharmacologic blockade. The most important questions in these patients are: (1) Is there a full third nerve palsy or are the findings confined to the pupillary constrictor? (Fig. 21.5), and (2) Is there altered mental status or other neurologic findings?

I. FULL THIRD NERVE PALSY: ASSOCIATED PTOSIS AND PARALYSIS OF OCULAR MOVEMENTS

Because the third cranial nerve controls the levator palpebrae (which lifts the eyelid) and four of six eye muscles (medial, inferior, and superior rectus muscles and inferior oblique muscle), a full third nerve palsy causes a dilated pupil, ptosis, and ophthalmoplegia with the eye deviated outward and downward (see Fig. 21.5, *top row*). In patients with anisocoria, this has the following two important causes:

A. IPSILATERAL BRAIN HERNIATION (HUTCHINSON PUPIL)^{30,31}

These patients are in the midst of a neurologic catastrophe from an expanding unilateral cerebral mass that causes coma, damage to the ipsilateral third nerve (dilated pupil, ptosis, and ophthalmoplegia), and eventually damage to the contralateral cerebral peduncle (which may lead to the false localizing sign of hemiplegia on the *same* side of the lesion). Although the involvement of the extraocular muscles may be difficult to recognize, most patients have narrowing of the ipsilateral palpebral fissure and an eye that (if not dysconjugate) moves poorly during the vestibuloocular reflex (doll's-eye maneuver or response to calorics).

Examination of the pupils is essential in patients with acute neurologic catastrophes: (1) In patients with **head trauma** and acute **subdural hematomas**,

approximately 40% have anisocoria, and the dilated pupil is *ipsilateral* to the expanding mass approximately 90% of the time, just as Hutchinson suggested.³²⁻³⁵ In addition, the presence of anisocoria or absent light reaction in patients with subdural hematomas predicts a worse outcome after craniotomy (sensitivity = 63% to 69%, specificity = 70% to 88%, positive LR = 3.4; worse outcome = dependence on others, persistent vegetative state, or death)^{36,37}; (2) In patients with **coma** (i.e., Glasgow coma scale ≤ 7),³⁸ anisocoria of more than 1 mm increases the probability of an intracranial structural disorder (e.g., expanding hemispheric or posterior fossa mass; LR = 9.0, **EBM Box 21.1**), whereas preservation of light reactions in both pupils decreases the probability of a structural disorder (LR = 0.2) and thus makes metabolic encephalopathy more likely (e.g., drug overdose, hypoglycemia, sepsis, uremia, or other metabolic disorder); and (3) In patients with **stroke**, anisocoria and full third nerve palsy increases the probability of intracranial hemorrhage (LR = 3.2, see **EBM Box 21.1**), thus decreasing the probability of ischemic cerebral infarction.

B. POSTERIOR COMMUNICATING ARTERY ANEURYSM

The most common of all intracranial aneurysms, posterior communicating artery aneurysms present with ipsilateral third nerve palsy (thus dilating the pupil) up to 60% of the time.⁴⁵ It is essential to recognize this disorder promptly because of the risk of subsequent, devastating subarachnoid hemorrhage. Importantly, the abnormal pupil is almost always accompanied by at least some degree of ptosis and ophthalmoplegia (i.e., features of a full third nerve palsy; see **Fig. 21.5**); isolated anisocoria is rare.

In alert patients with new-onset third nerve palsy (i.e., at least some degree of ptosis and ophthalmoplegia), the presence of a normal pupil decreases the probability of an intracranial aneurysm or other compressive lesion (LR = 0.2, see **EBM Box 21.1**; see also Pupil-Sparing Rules in **Chapter 59**), although almost all patients with this finding now undergo noninvasive neurovascular imaging to exclude intracranial aneurysms.⁴⁶

2. THE TONIC PUPIL

A. THE FINDING

The tonic pupil has five important features (**Fig. 21.6**): (1) unilateral dilation of a pupil, (2) poor or absent response to light, (3) extensive, slow (over seconds), and long-lasting constriction during near vision (this is why the pupil is called “tonic”; i.e., it is analogous to myotonia), (4) disturbances of accommodation (which causes the main concern for many patients [i.e., inability of the involved eye to focus]), and (5) supersensitivity of pupillary constriction to pilocarpine.^{25,47,48}

Although both the Argyll Robertson pupil and the tonic pupil display light-near dissociation, they are easily distinguished by the characteristics in **Table 21.1**.

B. PATHOGENESIS

The tonic pupil occurs because of injury to the ciliary ganglion and postganglionic fibers (see **Fig. 21.1**) and subsequent misdirection of nerve fibers as they regenerate from the ciliary ganglion to the eye. In the normal eye the ciliary ganglion sends 30 times the number of nerve fibers to the ciliary body (the muscle that focuses the lens during the near synkinesis) as to the iris (i.e., the pupillary constrictor).⁴⁹ After these fibers are disrupted, odds are thus 30 to 1 that the iris will receive regenerating fibers originally intended for the ciliary body instead of those participating in the light reaction. The pupil of these patients thus fails to respond to light, although during near vision, which normally activates the ciliary body, the misdirected fibers to the iris cause the pupil to constrict (i.e., light-near dissociation).



EBM BOX 21.1

*Pupils and Anisocoria**

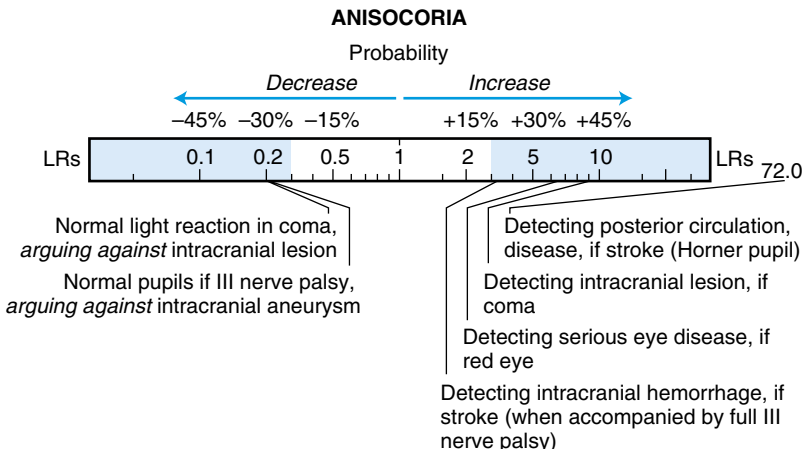
Finding (Reference)	Sensitivity (%)	Specificity (%)	Likelihood Ratio† if Finding Is	
			Present	Absent
Detecting Intracranial Structural Lesion in Patients With Coma ³⁸				
Anisocoria >1 mm	39	96	9.0	0.6
Absent light reflex in at least one eye	83	77	3.6	0.2
Detecting Intracranial Hemorrhage in Patients With Stroke ³⁹				
Anisocoria and full third nerve palsy	34	90	3.2	0.7
Detecting Intracranial Aneurysm in Patients With Third Nerve Palsy ⁴⁰⁻⁴²				
Anisocoria or abnormal light reaction	80-93	62-75	2.4	0.2
Detecting Serious Eye Disease in Patients With Unilaterally Red Eye ⁴³				
Anisocoria ≥1 mm	19	97	6.5	0.8
Detecting Posterior Circulation Disease in Patient With Stroke				
Horner syndrome ⁴⁴	4	100	72.0	NS

*Diagnostic standard: for *structural lesion*, supratentorial and subtentorial lesions with gross anatomic abnormality, including cerebrovascular disease, intracranial hematoma, tumor, and contusion; for *intracranial hemorrhage*, computed tomography; for *intracranial aneurysm*, contrast arteriography or rupture⁴² or CT/MRI angiography^{40,41}; for *serious eye disease*, corneal foreign body or abrasion, keratitis, or uveitis; for *posterior circulation stroke* (vs. anterior circulation), magnetic resonance imaging.

[†]Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.

CT, Computed tomography; MRI, magnetic resonance imaging; NS, not significant.

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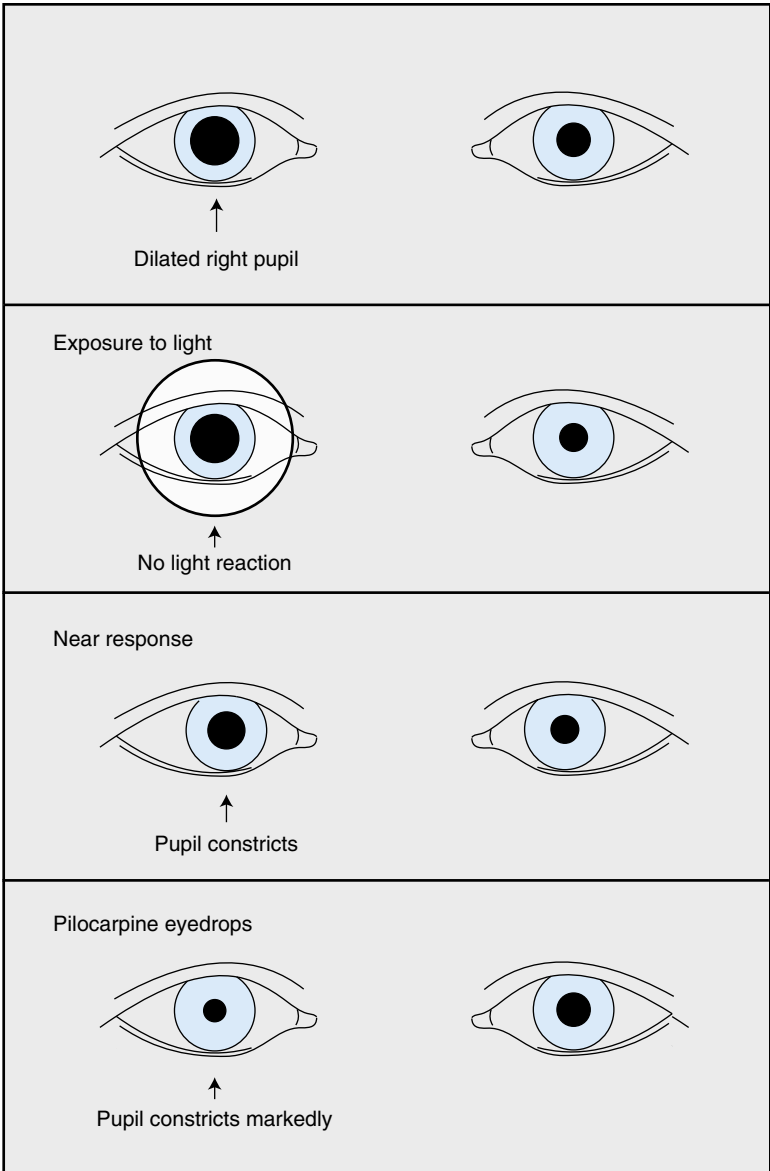


FIG. 21.6 TONIC PUPIL (ADIE PUPIL). The patient in this figure has a *right* tonic pupil. At baseline, there is anisocoria with the right pupil larger than the left (*first row*). The dilated pupil fails to react to light (*second row*) but constricts slowly (i.e., tonic contraction) when the patient focuses on a near object (*third row*). After instillation of dilute pilocarpine eyedrops (*fourth row*), the pupil constricts markedly.

Table 21.1 Comparison of Tonic Pupil and Argyll Robertson Pupil*

Finding	Tonic Pupil	Argyll Robertson Pupil
Pupil size	Large	Small
Laterality	Mostly unilateral	Mostly bilateral
Reaction to near vision	Extremely slow and prolonged with slow redilation	Normal with brisk redilation

*Based upon reference 47.

C. CLINICAL SIGNIFICANCE

Because the ciliary ganglion and postganglionic fibers are contiguous to the eyeball, a variety of local disorders cause the tonic pupil, including orbital trauma, orbital tumors, or varicella-zoster infections of the ophthalmic division of the trigeminal nerve. However, most cases are idiopathic, a condition dubbed the **Adie pupil** (named after William John Adie, although the syndrome was more thoroughly and accurately described by others before his 1931 paper).⁴⁷

3. DISORDERS OF THE IRIS

A. PHARMACOLOGIC BLOCKADE OF THE PUPIL WITH TOPICAL ANTICHOLINERGIC DRUGS

Pharmacologic blockade causes an isolated fixed, dilated pupil without paralysis of eye movements. Not all patients with this problem are surreptitiously instilling mydriatic drops. Causes include unintended exposure of the eye to anticholinergic nebulizer treatments,⁵⁰ scopolamine patches,⁵¹ and plants containing anticholinergic substances (blue nightshade, angel's trumpet, jimsonweed, moonflower).⁵² Nebulizer treatments are an important cause to recognize in the intensive care unit, where metabolic encephalopathy is also common, leading clinicians to misdiagnose the Hutchinson pupil in patients with pharmacologic anisocoria and unresponsiveness.

The pharmacologic pupil characteristically fails to constrict to topical pilocarpine.

4. THE POORLY REACTIVE PUPIL—RESPONSE TO PILOCARPINE

In difficult diagnostic problems, especially when pharmacologic blockade is a consideration, the pupil's response to topical pilocarpine solution is helpful. Pilocarpine constricts Adie pupil and the dilated pupil from parasympathetic denervation (Hutchinson pupil or intracranial aneurysm) but not the dilated pupil from pharmacologic blockade.⁵³

D. ABNORMAL PUPILLARY DILATOR

I. DEFINITION

The most important cause of an abnormal pupillary dilator muscle is sympathetic denervation of the pupil, or **Horner syndrome**, which has three characteristics: (1) ipsilateral miosis (paralyzed pupillodilator muscle), (2) ipsilateral ptosis (paralyzed superior tarsal muscle), and (3) ipsilateral anhidrosis of the face (from damage to sudomotor fibers). Sometimes, an elevated lower lid creates the appearance of enophthalmos, although the eye is not actually retracted. Fig. 21.7 describes the neuroanatomy of the sympathetic pathways innervating the eye.

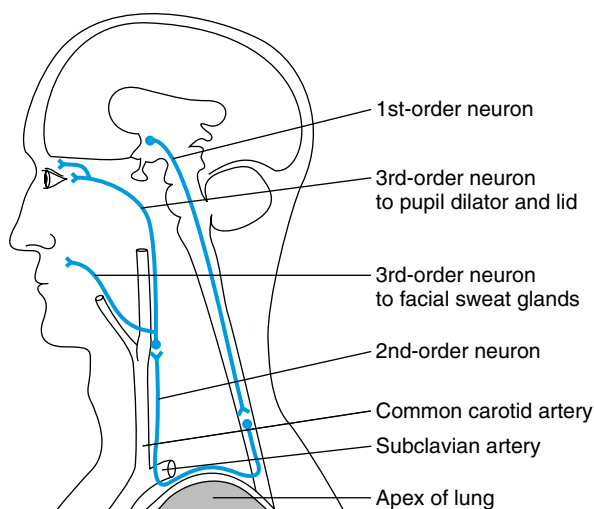


FIG. 21.7 ANATOMY OF SYMPATHETIC PATHWAYS TO THE EYE. The sympathetic innervation of the eye consists of three neurons connected in series: first-order neurons, second-order neurons, and third-order neurons. The first-order neurons (central neurons) extend from the posterior hypothalamus to the C8 to T2 level of the spinal cord. The second-order neurons (preganglionic neurons) leave the spinal cord and travel over the lung apex, around the subclavian artery, and along the carotid artery to the superior cervical ganglion. The third-order neurons (postganglionic neurons) diverge and take two paths: those to the pupil and lid muscles travel along the internal carotid artery through the cavernous sinus to reach the orbit; those to the facial sweat glands travel with the external carotid artery to the face. Lesions in any of these neurons cause Horner syndrome and distinct associated physical signs (see Fig. 21.3 and text).

Horner syndrome is named after the Swiss ophthalmologist Johann Horner, who described the syndrome in 1869, but like other eponymous pupillary findings (Adie pupil and Marcus Gunn pupil), earlier published descriptions of the finding exist.⁵⁴

2. HORNER SYNDROME VERSUS SIMPLE ANISOCORIA

When evaluating a pupil that dilates abnormally (left half of Fig. 21.3; patient 2 in Fig. 21.4), the findings of anisocoria greater than 1 mm, associated ptosis, or asymmetric facial sweating indicates Horner syndrome.

In difficult cases the definitive test of sympathetic denervation is the cocaine test (cocaine drops diminish the anisocoria of simple anisocoria but aggravate that of Horner syndrome; Fig. 21.8).⁵⁵ In one study of 169 persons the presence of post-cocaine anisocoria of 1 mm or more was pathognomonic for Horner syndrome (LR = 96.8; EBM Box 21.2) and its absence made Horner syndrome unlikely (LR = 0.1).

Nonetheless, cocaine eyedrops are difficult to obtain and store, and they render urine drug tests positive for up to 48 hours.⁵⁶ An alternative agent is apraclonidine, a topical glaucoma eyedrop that dilates the Horner pupil but not normal ones,⁵⁷ causing the anisocoria to actually reverse sides in patients with Horner syndrome (see Fig. 21.8). When compared with the cocaine eyedrop test, the apraclonidine eyedrop test is quite accurate: sensitivity 95%, specificity 90% to 95%, positive LR = 14, negative LR = 0.1; see EBM Box 21.2).

Because the apraclonidine response relies on sympathetic denervation supersensitivity, the test may be falsely negative early after onset of Horner syndrome before

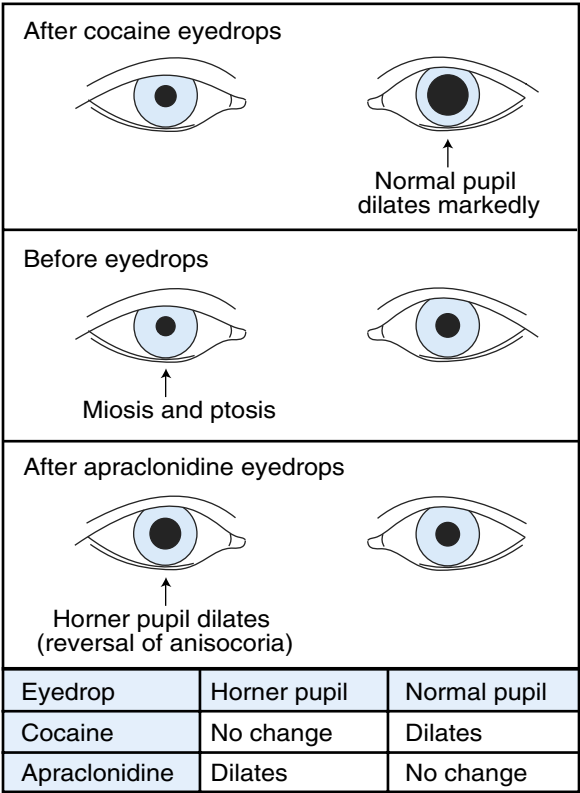


FIG. 21.8 CONFIRMATION OF HORNER SYNDROME: THE COCAINE AND APRA-CLONIDINE EYEDROP TESTS. This patient has a right Horner syndrome with right miosis and ptosis (*middle row*). Forty-five minutes after installation of cocaine drops into each eye (*top row*), the Horner pupil fails to dilate but the normal pupil dilates, markedly aggravating the anisocoria and confirming the diagnosis of Horner syndrome. Forty-five minutes after installation of apraclonidine drops into each eye (performed on a different day than the cocaine test, *bottom row*), the right Horner pupil dilates but there is no response in the normal pupil, thus reversing the anisocoria and also confirming the diagnosis of Horner syndrome. Cocaine eyedrops block the reuptake of norepinephrine at the myoneural junction of the iris dilator, causing the pupil to dilate unless norepinephrine is absent because of sympathetic denervation. Apraclonidine eyedrops have no effect on normal pupils, but after sympathetic denervation from Horner syndrome the affected pupil is supersensitive to their effect. Apraclonidine may also cause elevation of the lid in Horner syndrome (*bottom row*), although only the response of the pupil is used when interpreting the test.

supersensitivity has had time to develop. Nonetheless, one patient with Horner syndrome from a lateral medullary infarct developed a positive apraclonidine test just 36 hours after symptom onset.⁶⁶

3. CLINICAL SIGNIFICANCE OF HORNER SYNDROME

A. ETIOLOGY

Which etiologies of Horner syndrome a clinician is likely to see depends on the clinician's specialty. On a neurologic service, 70% of patients with Horner syndrome

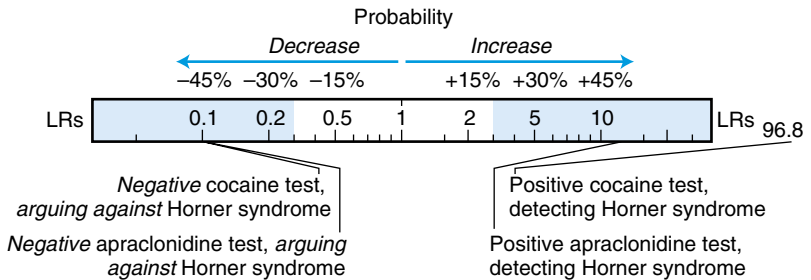
**EBM BOX 21.2***Horner Syndrome, Eyedrop Tests**

Finding (Reference)	Sensitivity (%)	Specificity (%)	Likelihood Ratio† if Finding Is	
			Present	Absent
Detecting Horner Syndrome				
Anisocoria ≥1 mm after topical cocaine) ^{58,59}	95	99	96.8	0.1
Reversal of anisocoria after topical apracloni- dine ^{60,61}	95	90-95	14.0	0.1
Diagnosing First or Second Order Nerve Lesion in Horner Syndrome				
Small pupil dilates with topical hydroxyamphet- amine (Paredrine) ^{62,63}	83-92	79-96	9.2	0.2
Small pupil fails to dilate with dilute phenyl- ephphrine ⁶⁴	88	79	4.2	NS
Asymmetric facial sweating ⁶⁵	53	78	NS	0.6

*Diagnostic standard: for *Horner syndrome* (cocaine drop testing), combined clinical follow-up and dilation lag of pupil during infrared video recording^{58,59}; for *Horner syndrome* (apraclonidine drop testing), cocaine drop testing^{60,61}; for *localization of Horner syndrome*, clinical evaluation^{62,63}, clinical evaluation plus Paredrine testing⁶⁵, or magnetic resonance imaging.⁶⁴

[†]Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, not significant.

[Click here to access calculator](#)

HORNER SYNDROME: EYEDROP TESTS

have lesions in the first-order neuron, usually strokes in the brainstem (see Table 62.2 in Chapter 62).⁶⁷ On a medical service, 70% of afflicted patients have lesions in the second-order neuron, usually from tumors (e.g., lung and thyroid) or trauma (e.g., to the neck, chest, spinal nerves, subclavian or carotid arteries).⁶⁸ Causes of third-order neuron lesions are vascular headache, carotid artery dissection, skull fracture, and cavernous sinus syndrome.

B. LOCALIZING THE LESION

(1). ASSOCIATED FINDINGS. Helpful features include the following: (1) findings from the ipsilateral brainstem (e.g., lateral medullary syndrome), pointing to a first-order neuron lesion (see Table 62.2 in [Chapter 62](#)); in patients hospitalized with stroke, the finding of Horner syndrome is a compelling argument for a posterior (vertebrobasilar) circulation stroke (*not* anterior circulation stroke; LR = 72, see [EBM Box 21.1](#); see also [Chapter 61](#)); (2) abnormal chest or neck findings, a supraclavicular mass, or motor, reflex, or sensory findings of the ipsilateral C8 to T1 spinal roots, all pointing to the second-order neuron lesion; and (3) orbital trauma, orbital inflammation, migraine, or neck pain, pointing to a third-order neuron lesion. An acute *painful* Horner syndrome suggests dissection of the carotid artery.

(2). FACIAL SWEATING. The sudomotor sympathetic fibers to the face diverge from the sympathetic pathway at the bifurcation of the carotid artery and therefore do not accompany the sympathetic nerves to the pupil and lid. Therefore Horner syndrome from third-order neuron lesions would theoretically preserve facial sweating, whereas Horner syndrome from first- and second-order neurons would cause asymmetric facial sweating. However, in one study this finding lacked diagnostic value (LR not significant; see [EBM Box 21.2](#)).

(3). DISTINGUISHING THIRD NERVE LESIONS FROM FIRST AND SECOND NERVE LESIONS: THE EYEDROP TESTS. When the cause of Horner syndrome remains unexplained despite careful bedside examination, most clinicians now routinely order magnetic resonance imaging to investigate the entire sympathetic pathway to the eye. However, before the advent of modern neuroimaging, eyedrop tests were used to distinguish first and second nerve lesions from third nerve lesions. The classic eyedrop test was the Paredrine test (i.e., topical hydroxyamphetamine). Dilatation of the Horner miotic pupil after topical Paredrine indicates a first- or second-order neuron lesion (LR = 9.2; see [EBM Box 21.2](#)). However, Paredrine is now difficult to obtain, and some investigators have recommended substituting diluted phenylephrine eyedrops (in this test the *absence* of dilation of the Horner miotic pupil after topical phenylephrine indicates a first- or second-order neuron lesion; LR = 4.2; see [EBM Box 21.2](#)).

E. INTRAOCULAR INFLAMMATION

As part of the eye's response to intraocular inflammation, the ipsilateral pupil often constricts. In one study of 317 patients with the unilaterally red eye, anisocoria of 1 mm or more (with the smaller pupil in the red eye) significantly increased the probability of serious eye disease (i.e., corneal foreign body, corneal abrasion, keratitis, or uveitis; LR = 6.5; see [EBM Box 21.1](#)) and thus decreased the probability of more benign problems (i.e., subconjunctival hemorrhage, conjunctivitis, or episcleritis). The absence of anisocoria was unhelpful (LR = 0.8).

V. DIABETES AND THE PUPIL

The pupils of patients with long-standing diabetes show signs of sympathetic denervation (small size and poor dilation in darkness), parasympathetic denervation (sluggish light reaction), and decreased amplitude of hippus.⁶⁹ However, denervation alone does not explain all of the diabetic pupillary abnormalities because the pupils of many patients also respond poorly to dilating and constricting eyedrops, a finding suggesting additional problems in the iris itself (i.e., denervated pupils are classically supersensitive to eyedrops).⁷⁰ Some reviews state that diabetes causes the Argyll Robertson pupil, but the data for this are meager and what exists suggests that the finding is very rare.¹⁷

VI. PINPOINT PUPILS AND ALTERED MENTAL STATUS

In one study of patients with altered mental status, the finding of pinpoint pupils predicted a positive response to naloxone (LR = 8.5), thus confirming the diagnosis of opiate intoxication.⁷¹ The absence of pinpoint pupils argued strongly against opiate intoxication (LR = 0.1).

The references for this chapter can be found on www.expertconsult.com.

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